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Treg Immunotherapy in Crohn’s Disease

Submission date 03/04/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 22/05/2017	**Overall study status** Completed	
Last Edited 27/09/2024	**Condition category** Digestive System	

Plain English summary of protocol

Current plain English summary as of 01/12/2022:
Background and study aims
Inflammatory bowel disease (IBD) is a term used to describe conditions which cause long-term inflammation (swelling) in the gut. The two main forms of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). Crohn’s disease can affect any part of the gut but is most commonly at the end of the ileum (the last part of the small intestine) or the colon (the large intestine). Crohn's disease is a long-term (chronic) condition. There is currently no cure, and so the main aim of treatment is to reduce the symptoms (remission) and prevent the disease from “flaring up” and becoming active again. The TRIBUTE trial is looking at a new type of treatment for Crohn’s Disease called regulatory T-cells (Tregs) immunotherapy. Regulatory T-cells are naturally produced by the immune system to modulate the immune system and prevent autoimmune disease (where the immune system mistakenly attacks the body's own healthy tissue). Treg immunotherapy will be unique to each patient. White blood cells will be extracted from their blood using a process in which blood is removed from the body and passed through a filter to remove white blood cells (including Tregs) before being returned to the body. These cells will be used to create Treg immunotherapy. The aim of this study is to assess the safety of regulatory T-cells (Tregs) immunotherapy in patients with Crohn's disease.

Who can participate?
Adults who have been diagnosed with moderate to severe Crohn's disease who did not tolerate or respond to at least 2 standard treatments.

What does the study involve?
Participants will be asked to attend visit the hospital several times to assess if they are eligible to take part. This is known as the screening process. This will involve assessing their general health and also a colonoscopy and radiological scan. If the study doctor confirms the participant can proceed, they will be asked to donate some white blood cells using a process called leukapheresis. The donated cells will be used to manufacture the Treg immunotherapy in the laboratory. The screening process and manufacture will take between 8-12 weeks. Once complete, participants will be asked to visit the hospital again to receive an infusion (drip) of the Treg immunotherapy. After the treatment, participants will be asked to stay overnight so study doctors can monitor how safe the treatment is and how the body reacts to Treg immunotherapy. Participants will then be asked to return to the hospital for regular follow-up visits to check how they are feeling. The safety of the therapy will be monitored by checking vital signs and blood

tests, asking participants to complete symptom diaries and questionnaires and one further colonoscopy.

What are the possible benefits and risks of participating?
There are currently no known benefits to the participants in taking part in the study, however, it is hoped that the treatment will reduce bowel inflammation. Participants may not directly benefit from taking part in this study but the information gained from their participation may help to improve the treatments available to other people with Crohn's Disease. During the blood tests participants may experience discomfort and there is a risk of bleeding and bruising around the puncture site but this is very rarely serious. The anticipated risks of Treg administration are similar to those of a blood transfusion. The potential risks are likely to be lower because the cells infused will be the patient's own cells rather than cells from a blood donor. Common side effects may include a red, itchy skin rash, swelling of the hands, arms, feet, ankles and legs, dizziness and headaches. Less common side effects include high temperature, chills and shivering.

Where is the study run from?
Guy's Hospital (UK)

When is the study starting and how long is it expected to run for?
August 2018 to June 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Professor Graham Lord (scientific)
2. Dr Peter Irving (public)
TRIBUTE@gstt.nhs.uk

Previous plain English summary:
Background and study aims
Inflammatory bowel disease (IBD) is a term used to describe conditions which cause long-term inflammation (swelling) in the gut. The two main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease can affect any part of the gut, but is most commonly at the end of the ileum (the last part of the small intestine) or the colon (the large intestine). Crohn's disease is a long-term (chronic) condition. There is currently no cure, and so the main aim of treatment is to reduce the symptoms (remission) and prevent the disease from "flaring up" and becoming active again. The TRIBUTE trial is looking at a new type of treatment for Crohn's Disease called regulatory T-cells (Tregs) immunotherapy. Regulatory T-cells are naturally produced by the immune system to modulate the immune system and prevent autoimmune disease (where the immune system mistakenly attacks the body's own healthy tissue). Treg immunotherapy will be unique to each patient. White blood cells will be extracted from their blood using a process in which blood is removed from the body and passed through a filter to remove white blood cells (including Tregs) before being returned to the body. These cells will be used to create the Treg immunotherapy. The aim of this study is to assess the safety and effectiveness of regulatory T-cells (Tregs) immunotherapy in patients with crohn's disease.

Who can participate?
Adults who have been diagnosed with moderate to severe crohn's disease who did not tolerate or respond to at least 2 standard treatments.

What does the study involve?
Participants are randomly allocated to receive two treatments spaced eight weeks apart in a random order. The first treatment involves receiving an infusion (drip) of Treg immunotherapy, and the second involves an infusion of a placebo (dummy drug). After both treatments, participants attend regular follow-up at which blood samples are taken to monitor how safe the treatment is and how the body reacts to Treg immunotherapy.Other tests, including vital signs such as blood pressure, heart rate and temperature, stool testing, and colonoscopy (a test that allows the inner lining of your large intestine to be viewed) are also performed for this purpose and participants will have regular check-ups by the trial team. Scans such as CT scans, MRI scans or ultrasounds may be performed prior to starting the trial and participants fill out questionnaires and diaries to monitor their progress over the course of the trial.

What are the possible benefits and risks of participating?
There are currently no known benefits to the participants in taking part in the study, however it is hoped that the treatment will reduce bowel inflammation. Participants may not directly benefit from taking part in this study but the information gained from their participation may help to improve the treatments available to other people with Crohn's Disease. During the blood tests participants may experience discomfort and there is a risk of bleeding and bruising around the puncture site but this is very rarely serious. The anticipated risks of Treg administration are similar to those of a blood transfusion. The potential risks are likely to be lower because the cells infused will be the patient's own cells rather than cells from a blood donor. Common side effects may include a red, itchy skin rash, swelling of the hands, arms, feet, ankles and legs, dizziness and headaches. Less common side effects include high temperature, chills and shivering.

Where is the study run from?
1. Guy's Hospital (UK)
2. St Thomas' Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2016 to June 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
1. Professor Graham Lord (scientific)
2. Dr Peter Irving (public)
TRIBUTE@gstt.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Prof Graham Lord

ORCID ID
https://orcid.org/0000-0003-2069-4743

Contact details
Lord Lab
Department of Experimental Immunobiology
Division of Transplantation Immunology and Mucosal Biology
5th floor Tower Wing
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT
+44 20 7188 3053
graham.lord@kcl.ac.uk

Type(s)
Public

Contact name
Dr Peter Irving

ORCID ID
https://orcid.org/0000-0003-0972-8148

Contact details
Department of Gastroenterology,
St Thomas' Hospital,
1st Floor, College House, Westminster Bridge Road
London
United Kingdom
SE1 7EH
+44 20 7188 2499
peter.irving@kcl.ac.uk

Type(s)
Scientific

Contact name
Dr Joanne Palmer Joyce

Contact details
Head of the Clinical Trial Management Research Platform
Trial manager
Guys and St Thomas' NHS Foundation Trust
16th Floor Tower Wing
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT
+44 (0)7793020617
joanne.palmerjoyce@gstt.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2017-000170-11

ClinicalTrials.gov (NCT)
NCT03185000

Protocol serial number
Nil known

Study information

Scientific Title
A first-in-human feasibility study of T regulatory cells (TR004) for inflammatory bowel disease using (ex vivo) Treg expansion

Acronym
TRIBUTE

Study objectives
Tregs will “reset” the balance of the immune system and thus provide a treatment for patients with moderate to severe Crohn’s Disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/05/2022, North East - York Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8079; york.rec@hra.nhs.uk), Ref: 22/NE/0062

Study design
Open-label first-in-human single-dose feasibility study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Crohn's Disease

Interventions
Current interventions as of 01/12/2022:
Four participants will receive a single dose of TR004. Participants will be dosed singly. Safety data will be collected for five weeks post-administration and reviewed by the DSMB before

proceeding to dose the next participant. All participants will be followed up to week 21 to collect further safety and exploratory efficacy data, with additional safety monitoring at 1 and 2 years post-dose.

Patients randomised to AP will receive TR004 at Week 0 and Placebo at Week 8. Patients allocated to PA will receive Placebo at Week 0 and TR004 at Week 8.

There will be 3 dose levels for TR004: 0.5 – 1.0 x 10^6 TR004/kg, 3.0 – 5.0 x 10^6 TR004/kg and 8.0 – 10.0 x 10^6 TR004/kg.

The first pair on the trial will be dosed at 0.5 – 1.0 x 10^6 TR004/kg. The CRM algorithm program will allocate dose levels for subsequent pairs. The information will be reviewed during the DSMB meetings in order to agree on the dose level for the next pairs. Both TR004 and Placebo will be administered intravenously over 30 minutes maximum.

On dosing days, patients will be closely monitored. Blood tests and vital signs will be taken at specific time points throughout the day. At Week 8, patients will also have a colonoscopy and biopsy. Patients will be discharged from the hospital the day after dosing unless there are any safety concerns.

Patients will then attend outpatient follow-up visits at Weeks 1, 2, 3, 5, 9, 10, 11, 13, 16, 21 and 52 (safety FUP). During these visits, patients will be reviewed by a doctor who will examine them and asks questions about how they have been feeling, any events/reactions they may want to report or any changes in their regular medications. Clinical and research blood tests will be taken to monitor safety following the infusions and potential response to treatment. Blood pressure, heart rate, oxygen saturation, temperature and weight will be measured to monitor safety. Stool samples will be collected in order to measure inflammation markers and any potential changes from baseline. Patients will complete quality-of-life questionnaires in order to identify potential changes from baseline. At Week 16, patients will also have a colonoscopy and biopsy.

Previous interventions:
Patients will be block randomised in a two-period crossover design to the order in which they receive both TR004 and placebo. In each successive pair of subjects, one will first receive TR004 (autologous GMP- expanded regulatory T cells) and the other will first receive placebo at the same dose as each other and in each period. Eligible patients will receive a single dose of TR004 and a single dose of placebo, either at Week 0 or Week 8, depending on randomisation allocation.

Patients randomised to AP will receive TR004 at Week 0 and Placebo at Week 8.
Patients allocated to PA will receive Placebo at Week 0 and TR004 at Week 8.

There will be 3 dose levels for TR004: 0.5 – 1.0 x 10^6 TR004/kg, 3.0 – 5.0 x 10^6 TR004/kg and 8.0 – 10.0 x 10^6 TR004/kg.

The first pair on the trial will be dosed at 0.5 – 1.0 x 10^6 TR004/kg. Dose levels for subsequent pairs will be allocated by the CRM algorithm program. The information will be reviewed during the DSMB meetings in order to agree the dose level for the next pairs. Both TR004 and Placebo will be administered intravenously over 30 minutes maximum.

On dosing days, patients will be closely monitored. Blood tests and vital signs will be taken at specific time points throughout the day. At Week 8, patients will also have a colonoscopy and biopsy. Patients will be discharged from hospital the day after dosing, unless there are any safety concerns.

Patients will then attend outpatient follow-up visits at Week 1, 2, 3, 5, 9, 10, 11, 13, 16, 21 and 52 (safety FUP). During these visits, patients will be reviewed by a doctor who will examine them and asks questions about how they have been feeling, any events/reactions they may want to report or any changes in their regular medications. Clinical and research blood tests will be taken to monitor safety following the infusions as well as a potential response to treatment. Blood pressure, heart rate, oxygen saturation, temperature and weight will be measured to monitor safety. Stool samples will be collected in order to measure inflammation markers and any potential changes from baseline. Patients will complete quality of life questionnaires in order to identify potential changes from baseline. At Week 16, patients will also have a colonoscopy and biopsy.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
TR004 (autologous GMP- expanded regulatory T cells)

Primary outcome(s)
Current primary outcome measure as of 01/12/2022:
Number of dose-limiting toxicities measured using the criteria defined in the protocol for 24 hours post-dosing, and at weeks 1, 2, 3 and 5 safety follow-up visits

Previous primary outcome measures:
1. Rate of dose limiting toxicities (DLTs) occurring 5 weeks post-infusions – two periods will be assessed, from Week 0 to Week 5 and from Week 8 to Week 13
2. Determination of Maximum Tolerated Dose (MTD), defined as the dose associated with a target DLT rate of 25%, is assessed by recording the rate of DLTs occurring between W0 and W5 and between W8 and W13

Key secondary outcome(s))
Current secondary outcome measures as of 01/12/2022:

Feasibility Outcomes
1. Amount of TR0004 manufactured per patient at the end of the manufacturing period
2. Number of participants recruited within the duration of the trial
3. Number of study visits completed per patient
4. Responses to items in questionnaires or surveys exploring the experience of the participants once they have completed the trial, and the trial team and DSMB members when the trial has ended. This will not form part of the final trial report. Qualitative data collection and any data analysis will be separate from the trial.

Secondary Outcomes
1. Assessment of clinical response:

1.1. Disease Activity Score measured by calculating Crohn's Disease Activity Index (CDAI)/Patient-Reported Outcome (PRO-2) at week 0 and 8
1.2. Biomarkers analysis:
1.2.1. Serum C reactive protein (CRP) levels will be measured by analysis of blood samples taken at all study visits
1.2.2. Faecal calprotectin (FCP) levels will be measured by analysis of stool samples taken at all study visits (except Day 0 and 1 of week 0)
1.3. Mucosal healing response measured by calculating SES-CD scores at screening and week 8
2. Assessment of immunological response measured by analysing blood samples taken at screening, and weeks 0, 1, 2, 3, 5, 8, 16 and 21:
2.1. Numbers and functions of Tregs
2.2. Measurement of deuterium-enriched cells
2.3. Cytokine levels
2.4. Comparison of circulating and localised cells to determine differences and similarities
3. Adverse events that do not meet the criteria of dose-limiting toxicity as defined in the protocol will be recorded for the duration of the study and summarised

Previous secondary outcome measures:
Clinical Response is assessed at baseline, 8 and 16 weeks by measuring:
1. Disease Activity Score (CDAI / PRO-2) calculated by evaluation of the parameters reported on the patient's diary and colonoscopy findings
2. Biomarkers analysis (CRP, FCP) measured by blood test and stool sample analysis
3. Mucosal Healing Score (CDEIS / SES-CD) calculated by evaluation of colonoscopy findings

Exploratory Outcomes:
1. Minimum Effective Dose (MED) of TR004, defined as the dose at which at least 1 patient out of 6 patients treated at the same dose level has demonstrated a within-patient efficacy response set out as being a reduction in CDAI of at least 100 points over 8 weeks from TR004 infusion
2. Immunological Response is assessed at Week 1, 2, 3, 5, 9, 10, 11, 13, 16 and 21 by measuring:
2.1. Lymphocyte populations circulating in blood as well as localised in the intestinal lamina propria, as measured by analysis of translational research blood samples
2.2. Cytokine levels in blood and in intestinal lamina propria, as measured by analysis of translational research blood samples
2.3. Differences and similarities in circulating and localised cells, as measured by analysis of translational research blood samples
2.4. Levels of circulating regulatory T cells labelled with Deuterium in blood, as measured by analysis of translational research blood samples
2.5. Microbiome is assessed using stool samples

Completion date
30/06/2025

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 01/12/2022:
1. Able and willing to provide written informed consent and able to comply with the protocol requirements
2. Male or female aged between 18 and 80 (inclusive) years of age at the date of consent
3. A diagnosis of Crohn's disease (CD) established ≥12 weeks prior to the date of consent by

standard clinical, radiological, endoscopic and histological criteria
4. Documented moderate to severe CD with a Crohn's Disease Activity Index (CDAI) 220 within 3 months of the date of consent
5. Active CD (mucosal inflammation) including ulceration, as assessed by colonoscopy at screening
6. Failure to tolerate or to respond, or lose response to at least 2 prior lines of standard CD medication intended to induce or maintain remission, as determined by the referring gastroenterologist. Examples of such medications include, but are not limited to, azathioprine, mercaptopurine, methotrexate, vedolizumab, ustekinumab or anti-tumour necrosis factor antibody therapy. This does not include steroids and 5-ASA medications
7. Stable doses of concomitant medications, as defined in Section 5.6
8. Normal or non-clinically significant electrocardiogram (ECG), as assessed by the Investigator at screening
9. Negative stool test for Clostridium difficile and faecal culture for standard pathogens at screening. For non-pathogenic organism, inclusion will be at the discretion of the Principal Investigator (PI).
10. Negative serology for HIV – 1/2, Hepatitis B (cAb and sAg), Hepatitis C, HTLV and Syphilis at screening
11. Patient is judged by the Chief Investigator to be in otherwise good health based upon the results of all screening investigations in combination with medical history and physical examination

Previous participant inclusion criteria:
1. Able and willing to provide written informed consent and able to comply with the protocol requirements
2. Male or female aged between 18 and 80 (inclusive) years of age
3. A diagnosis of Crohn's disease (CD) established ≥3 months prior to consent by standard clinical, radiological, endoscopic and histological criteria
4. Documented moderate-to-severe CD with a Crohn's Disease Activity Index (CDAI) 220 within 3 months of screening
5. Active CD (mucosal inflammation) including ulceration, as assessed by colonoscopy at screening
6. Failure to tolerate or to respond to at least 2 prior lines of standard CD medication intended to induce or maintain remission, as determined by the referring gastroenterologist. Examples of such medications include, but are not limited to, azathioprine, mercaptopurine, methotrexate or anti-tumour necrosis factor antibody therapy. This does not include steroids and 5-ASA medications
7. Stable doses of concomitant medications, as defined in Section 5.6
8. Normal or non-clinically significant electrocardiogram (ECG), as assessed by the Investigator at screening
9. Negative stool test for Clostridium difficile and faecal culture for standard pathogens at screening. For non-pathogenic organism, inclusion will be at the discretion of the Principal Investigator (PI)
10. Negative serology for HIV, Hepatitis B (cAb and sAg), Hepatitis C, HTLV and Syphilis at screening
11. Subject is judged by the principal investigator to be in otherwise good health based upon the results of all screening investigations in combination with medical history and physical examination
12. Clinical Blood Tests prior to dosing, assessed on Day-1 at Week 0 and Week 8:
12.1. Hb > 100g/L and WBC > 3.5 x 10^9/L and Plt > 100 x 10^9/L
12.2. Creatinine < 1.5x ULN
12.3. Total bilirubin ≤ 34 µmol/L and ALT ≤ 2x ULN and GGT ≤ 2xULN. Elevated unconjugated

bilirubin related to Gilbert's syndrome is allowed
13. Negative urine pregnancy test for female of childbearing potential prior to dosing, assessed on Day-1 at Week 0 and Week 8

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Total final enrolment
5

Key exclusion criteria
Current participant exclusion criteria as of 01/12/2022:
1. A diagnosis of ulcerative colitis or IBD-unclassified
2. CD treatment-naïve patients, defined as patients who have never received or have refused standard CD treatment
3. History of clinically significant drug or alcohol abuse in the last 12 months prior to the date of consent
4. Any history of major immune deficiency disorder, except Crohn's disease
5. Patients with a history of pulmonary embolism or deep vein thrombosis. Current or recent history (within 1 year prior to screening) of a major organ or system failure or condition, acute or chronic that in the opinion of the investigator should preclude enrolment, except Crohn's disease
6. History of intestinal resection or intra-abdominal surgery within 6 months prior to the date of consent
7. Requirement for immediate or imminent surgical, endoscopic or radiological intervention for indications including (but not limited to) toxic megacolon, obstruction, massive haemorrhage, perforation, sepsis, or intra-abdominal or perianal abscess
8. Patients with ileostomy or colostomy
9. Patients with short bowel syndrome (less than 1.5m of the small bowel)
10. Complications of Crohn's disease such as strictures/stenosis, penetrating disease, or any other condition that might require gastrointestinal surgery
11. Patients receiving therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to the date of consent and/or during the screening period
12. Patients who are currently using anticoagulants including but not limited to warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban (note that anti-platelet agents such as aspirin up to 325mg daily or clopidogrel are permitted)
13. Use of corticosteroids on the day of leukapheresis sampling, prior to the procedure

Dosing should be delayed until after the procedure has been completed. This must be checked prior to the appointment and rescheduled if use is confirmed.
14. Current medically significant infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to consent or oral anti-infectives for non-Crohn's disease-related infections within 14 days prior to consent
15. Participants with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the patient unsuitable for the study
16. History of tuberculosis (TB), unless there is documented evidence of completion of a full course of anti-TB treatment prior to screening. For patients with latent TB, as defined by a physician specialised in TB, they must have received prophylactic treatment for 4 weeks minimum prior to dosing
17. History of severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident (within 6 months of screening) and any other condition which, in the opinion of the investigator would put the patient at risk by participating in the study
18. Patient with a previous history (within 12 months of the consent) of dysplasia of the gastrointestinal tract, or found to have dysplasia during the screening endoscopy unless this is deemed to be a sporadic adenoma and has been completely removed
19. Significant laboratory abnormalities, assessed on Day-1 at Week 0:
19.1. Hb < 100g/L or WBC < 3.5 x 109/L or Plt < 100 x 109/L
19.2. Creatinine > 1.5x ULN
19.3. Total bilirubin > 34 µmol/L or ALT > 2x ULN or GGT > 2xULN. Elevated unconjugated bilirubin related to Gilbert's syndrome is allowed
These bloods will be initially reviewed at screening and if considered clinically significant, the patient will be excluded. If the CI considers it appropriate to proceed, any abnormalities identified at screening will be corrected as part of routine care before assessment prior to dosing at day -1, Week 0.
20. Anti-TNF or ustekinumab therapy within 8 weeks of dosing (day 0). Vedolizumab therapy within 5 half-lives (15 weeks) of dosing. Exposure to cyclosporine or tacrolimus within 2 weeks of consent
21. Patient currently receiving total parenteral nutrition (TPN) or plans to receive TPN at any time during the course of the study
22. Received another investigational drug within 60 days of the anticipated study date of consent or 5 half-lives whichever is greater
23. Patient who previously received stem cell transplantation
24. Current evidence of dysplasia or history of malignancy within the last 5 years of consent (except non-melanoma skin cancer, successfully treated squamous cell or basal cell carcinoma, without metastases or localised carcinoma in situ of the cervix)
25. Pregnant and lactating patients (females of childbearing potential with a positive serum pregnancy test at screening visit 1 or day -1 at week 0).
26. Female patients of childbearing potential who are not willing to use a highly effective method of contraception for the duration of the trial (defined as consent to W21 visit) to prevent pregnancy, or abstain from heterosexual activity.
*Females of child-bearing potential are females who have experienced menarche and are not surgically sterilised (e.g., hysterectomy, bilateral salpingectomy or bilateral oophorectomy) or post-menopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
** Highly effective methods of contraception are those with a failure rate of < 1% per year when employed consistently and correctly, e.g.
26.1. combined (oestrogen and progestogen containing) hormonal contraception associated

with inhibition of ovulation – oral, intravaginal, transdermal
26.2. transdermal progestogen-only hormonal contraception associated with inhibition of ovulation – oral, injectable, implantable
26.3. Intrauterine device (IUD)
26.4. Intrauterine hormone-releasing system (IUS)
26.5. Bilateral tubal occlusion
26.6. Vasectomised partner, provided that partner is the sole sexual partner of the FOCBP trial participant and that the vasectomised partner has received a medical assessment of the surgical success.
26.7. Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual activity from the date of consent until the week 21 visit. The reliability of this method should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
27. Male patients who are not willing to use an effective method of contraception (condoms), for the duration of the study (consent to W21 visit), when engaging in sexual activity with a female of childbearing potential
28. Allergy to any component / excipients used for the manufacture of TR004
29. Patient is considered by the Principal Investigator, for any reason, to be an unsuitable candidate for the study

Previous participant exclusion criteria:
1. A diagnosis of ulcerative colitis or IBD-unclassified
2. CD treatment-naïve patients, defined as patients who have never received or have refused standard CD treatment
3. History of clinically significant drug or alcohol abuse in the last 12 months
4. Any history of major immune deficiency disorder, except Crohn's disease
5. Patients with a history of pulmonary embolism or deep vein thrombosis. Current or recent history (within 1 year prior to screening) of major organ or system failure or condition, acute or chronic that in the opinion of the investigator should preclude enrollment, except Crohn's disease
6. History of intestinal resection or intra-abdominal surgery within 6 months prior to visit 1 (screening)
7. Requirement for immediate or imminent surgical, endoscopic or radiological intervention for indications including (but not limited to) toxic megacolon, obstruction, massive haemorrhage, perforation, sepsis, or intra-abdominal or perianal abscess
8. Patients with ileostomy or colostomy
9. Patients with short bowel syndrome (less than 1.5m of small bowel)
10. Complication of Crohn's disease such as strictures/stenosis, penetrating disease, or any other manifestation that might require surgery. Subject has received therapeutic enema or suppository, other than required for endoscopy, within 14 days prior to screening and/or during the screening period
11. Patients who are currently using anticoagulants including but not limited to warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban (note that anti-platelet agents such as aspirin up to 325mg daily or clopidogrel are permitted)
12. Current medically significant infection i.e. infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to screening or oral anti-infectives for non-Crohn's disease related infections within 14 days prior to screening visit
13. Subject with an active systemic viral infection or any active viral infection that based on the investigator's clinical assessment makes the subject unsuitable for the study
14. History of tuberculosis (TB), unless there is documented evidence of completion of a full course of anti-TB treatment prior to screening. For patients with latent TB, as defined by a physician specialised in TB, they must have received prophylactic treatment for 4 weeks

minimum prior to dosing
15. History of moderate to severe congestive heart failure (NYHA class III or IV), recent cerebrovascular accident (within 6 months of screening) and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study
16. Subject with a previous history of dysplasia of the gastrointestinal tract, or found to have dysplasia in any biopsy performed during the screening endoscopy or endoscopy performed within 45 days of baseline unless this is deemed to be a sporadic adenoma and has been completely removed
17. Significant laboratory abnormalities:
Hb < 100g/L or WBC < 3.5 x 10^9/L or Plt < 100 x 10^9/L
Creatinine > 1.5x ULN
Total bilirubin ≥ 34 µmol/L or ALT ≥ 2x ULN or GGT ≥ 2xULN. Elevated unconjugated bilirubin related to Gilbert's syndrome is allowed
18. Anti-TNF,vedolizumab or ustekinumab therapy within 8 weeks of study treatment initiation. Exposure to cyclosporine or tacrolimus within 2 weeks of anticipated study date of consent
19. Subject currently receiving total parenteral nutrition (TPN) or plan to receive TPN at any time during the course of the study
20. Received another investigational drug within 60 days of anticipated study date of consent or 5 half lives whichever is greater
21. Subject who previously received stem cell transplantation
22. Current evidence of dysplasia or history of malignancy within the last 5 years (except successfully treated squamous cell or basal cell carcinoma, without metastases or localised carcinoma in situ of the cervix)
23. Pregnant and lactating patients (females of childbearing potential must have a negative dipstick pregnancy test at study entry)
24. Female patients of childbearing potential (i.e. not post-menopausal or surgically sterilised) who are not willing to use effective methods of contraception (included but not limited to hormonal contraception, Intrauterine devices, sexual abstinence, vasectomised partner) to prevent pregnancy or abstain from heterosexual activity for the duration of the trial up to W21 visit
25. Male patients who are not willing to use an effective method of contraception (included but not limited to use of condom, vasectomy, sexual abstinence) for the duration of the study up to W21 visit, when engaging in sexual activity with a female of childbearing potential
26. Allergy to any component / excipients used for the manufacture of TR004
27. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study
28. Inability to comply with the study protocol

Date of first enrolment
08/08/2022

Date of final enrolment
30/11/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Guy’s Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
Guy's and St Thomas NHS Foundation Trust (GSTFT)

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Anonymised datasets generated during and/or analysed during the current study are/will be available upon request from the study Chief Investigator (Dr Peter Irving, Peter.Irving@gstt.nhs.uk).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet version 1	11/11/2025	11/11/2025	No	Yes
Protocol file		14/03/2022	01/12/2022	No	No